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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/713,008	11/17/2003	Masaaki Ikeda	64517.000002	5744

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EXAMINER	
GARVEY, TARA L	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 10/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/713,008	IKEDA ET AL.	
	Examiner	Art Unit	
	Tara L. Garvey	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *April 18, 2006 and July 18, 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-19* is/are pending in the application.

4a) Of the above claim(s) *4-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 16-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 2 and 4-19 are pending. Receipt is acknowledged of an amendment filed on July 18, 2006 in which claim 3 was canceled, claims 7-15 were withdrawn and new claims 18 and 19 were added.

Response to Amendment

Claim Objections

The objection of claims 2 and 4 is withdrawn in view of applicant's amendment.

Response to Arguments

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4-6 and 16-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of proliferating cardiomyocytes *in vitro* by introducing adenoviral vectors expressing a D-type cyclin, CDK4 or CDK 6 and a nuclear localization signal, does not reasonably provide enablement for an *in vitro or in vivo* method of proliferating any terminal differentiated cell by introducing any cyclin and any cyclin dependent kinase into the cell. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims for reasons of record as set forth in the office action mailed on November 18, 2005. **This rejection is applied to new claims 18 and 19, which is necessitated by applicants' amendment of the claims.**

Applicant's arguments filed April 18, 2006 have been fully considered but they are not persuasive.

(1) Applicant's argue that the Office action failed to establish a prima facie case that undue experimentation is required to make and use the instantly claimed invention.

In response to applicant's arguments, the Office action addressed all the applicable Wands factors in the enablement rejection. In particular, the Office action demonstrated the unpredictable nature of gene therapy (e.g. the technology used to carryout the claimed method of proliferating terminally differentiated cells), the lack of guidance in the specification to enable the full scope of the invention and the large amount of experimentation needed to determine all the factors to perform the entire scope of the claimed method.

(2) Applicant's argue that the Office used the incorrect legal standard in determining enablement since the patent application need only use art-accepted models of a disease or therapy and is not held to the same standards as the FDA as ruled in In re Brana. Further, in order to meet the enablement requirement, it is not necessary to teach how to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect.

In response to applicant's arguments, the Office has not required applicants to teach a perfected commercially viable embodiment or to be held to FDA standards. In addition, the conclusions from In re Brana were for a case based on utility and mainly for 35 U.S.C. 101.

(3) Applicant's argue that the Office action require that Applicants to enable every aspect of gene therapy, but the specification only needs to teach one method of effecting the claims and need not enable the full scope of the art.

In response to applicant's arguments, In re Fisher as cited in MPEP 2164.01(b) also states that the enablement requirement of 35 U.S.C. 112 is satisfied as long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim. In the instant case, the specification has only demonstrated the ability of D-type cyclins and CDK4 or CDK6 delivered to cardiomyocytes using adenoviral vectors. This one method does not provide a reasonable correlation for the entire scope of the claimed invention, which encompasses any terminal differentiated cell type.

(4) Further, Applicant's argue that the Office used the reverse of the legal standard when it stated that "the prior art did not compensate for the lack of guidance in the specification" because the specification solves problems present in the prior art. The instant specification demonstrates the induction of cell division in cardiomyocytes *in vivo* using a gene therapy method in Example 4 and thus, it is the specification and not the prior art that needs to provide guidance.

In response to applicant's arguments, the prior art can provide guidance for methods that are routine in the art. The statement in the Office action demonstrates that the art did not provide enablement for the claimed invention because methods involving gene therapy are not routine. Additionally, Example 4 provides for the induction of cell division of cardiomyocytes *in vitro* and not *in vivo*.

(5) In regard to the nature of the invention and breadth of the claim, applicant's argue that the specification provides sufficient disclosure on how to make and use a method of proliferating terminal differentiated cells comprising introducing a D-type cyclin and a CDK into the nucleus of terminal differentiated cells and cultivating or holding said cells.

In response to applicant's arguments, the amendment to the claims has narrowed the scope of the invention to a specific cyclins (i.e. D-type cyclins) and specific CDKs (i.e. CDK4 and CDK6) in response to the scope of enablement rejection.

(6) In regard to the guidance in the specification and existence of a working example, applicant's argue that they have solved the problem of inducing proliferation in cardiomyocytes without triggering apoptosis by introducing a cyclin D1 gene with a nuclear localization signal (NLS) and a CDK4 gene via an adenovirus vector into cultured cardiomyocytes. Further, the specification demonstrates that rats treated with recombinant adenovirus carrying D1NLS/CDK4 or the lacZ gene shows the expression of these genes demonstrating that the vehicle works in vivo. Tamamori-Adachi et al provides additional evidence. Applicant's further argue that this is an art-accepted model and therefore, they have met their burden of enablement in view of In re Brana.

The specification need not demonstrate every aspect of the invention but only show how to make and use the invention for the claims to be enabled.

In response to applicant's arguments, the specification and working examples have provided guidance for proliferation of cardiomyocytes using a cyclin D1 with a NLS and CDK4 that are delivered by an adenoviral vector, but the claimed scope of the invention is broader than the guidance provided in the specification. Although every aspect of the invention does not need to be disclosed in order to be enabled, in this situation, the disclosure of one cyclin/CDK combination delivered by one type of gene therapy vector into one type of cell does not reasonably provide enablement for all cell types, all cyclin/CDKs and all delivery methods. In regard to an art accepted model, the Tamamori-Adachi et al article provided by applicant's includes the inventors and the model disclosed is the same as that in the instant specification. Therefore, applicant's cannot conclude that providing their own work again constitutes an art accepted model. Additionally, the only disclosed use for delivery of the cyclin and CDK to cardiomyocytes *in vivo* is for treatment (specification, page 7, paragraph 0025). The experimental data in one mouse model for delivery to the heart is not enabling for treatment of other animals or diseases. In general, animal models are not always predictive of the results in humans. In one example, treatment success seen in small animal models for coronary artery disease was not predictive of success in humans (Johnson et al Thromb Haemost (1999) volume 81, pages 835-843; see page 835, left column and page 836 left column, first full paragraph). In addition, the conclusions from In re Brana were for a case based on utility and mainly for 35 U.S.C. 101.

(7) In regard to state of the art/predictability of the art, applicant's argue that the use of post-filing art is generally improper unless it is evidence that the disclosed invention was not possible at the time of filing. The Pagano and Jackson reference support the claims and thus do not provide evidence of unpredictability.

In response to applicant's arguments, the Pagano and Jackson reference does not support the claims and thus was properly used as post-filing art to demonstrate the unpredictability of the ability of specific cyclin and CDK pairings to produce a proliferative effect in all cell types. Further, the use of post-filing is not improper. It demonstrates the state of the art and fulfills one of the Wands factors. In addition applicant, must be enabled as of the effective filing date of the application.

(8) Applicant's argue that the Brooks and LaThangue reference does not provide evidence of unpredictability, but instead provides evidence that the art favored the claims because of the role cyclins play in the cell cycle. In regard to the assertion that cyclins and CDKs may result in deregulation of the cell cycle that can lead to tumorigenesis and hyperproliferation of cells, the applicant's argue that adenoviruses generally do not stably integrate the transgene into the host genome. This property of adenoviruses avoids the concern raised in the office action because the gene delivery vehicle would not cause tumorigenesis because integration is usually the cause of tumorigenesis in gene therapy. Additionally, adenoviruses show effective expression in both proliferating and non proliferating cells, avoiding this concern raise by the office action.

In response to applicant's arguments, the Brooks and LaThangue reference describe the role of aberrant expression of cyclins and CDKs in proliferative disease and potential methods to inhibit the cyclins and CDKs for treatment of proliferative disorders such as cancer and cardiovascular disease. The reference does not provide evidence that the art favored the claims, but rather demonstrates the harmful effect overexpression of cyclins and CDKs can have on the proliferative nature of cells. The reference provides support to the unpredictable nature of overexpression of these genes in cells and the potential to lead to deregulation of the cell cycle. The discussion of deregulation of the cell cycle in the Office action was referring to the potential problems caused by overexpression of cell cycle genes in the nucleus of a cell and not necessarily to the delivery vehicle. In regard to adenoviral vectors, even though they do not integrate, they are capable of high expression levels which can further pose potential problems in terms of uncontrolled proliferation. Additionally, the claims are not limited to using adenovirus or to the genes being transiently expressed. The specification teaches that other suitable vectors such as a retroviral vectors, which stably integrate into the genome can be used (see page 12, paragraph 048) and tumorigenesis caused by integration of the gene may become a factor. Finally, the applicant made a nice argument about the advantage of using adenoviral vectors, but the argument underscores and supports the scope of enablement rejection made. As mentioned previously, the claims do not limit the invention to the use of only adenoviral vectors and the applicant's arguments about avoiding the concerns about tumorigenesis

by using adenoviral vectors actually supports the scope of enablement rejection made of record in the previous office action.

(9) Applicant's argue that the Verma and Somia reference provide guidance on how to overcome the obstacles existing prior to the filing of the instant application and that the teachings of the instant application in conjunction with Verma and Somia provides adequate guidance to practice the claimed invention as instantly claimed. Further, Verma and Somia supports the specification as enabling because the specification was filed four years after Verma and Somia and they state that "in the not too distant future, gene therapy will become as routine as heart transplants are today."

In response to applicant's arguments, the reference provides a review of the characteristics that make and ideal vector for gene therapy and the problems associated with the vectors at that time. The reference does not provide a solution for all the problems associated with the vector technology. Further, the specification was only filed four years after Verma and Somia and many of the obstacles still existed at that time. Further, gene therapy by 2001 was still not routine as hypothesized by Verma and Somia; therefore, Verma and Somia does not provide enablement for the claimed invention.

(10) Applicant's argue that Marshall et al does not address the art nor provide information on the technology as it existed in 1995 since the article is an opinion article and is mostly concerned with ethical and political dimensions of gene therapy, which is outside the purview of the USPTO. The applicants have cited Juicy Whip Inc. v. Orange Bang Inc. decision.

In response to applicant's arguments, Marshall et al is more than an opinion article. The references addresses that at that time gene therapy was not successful, teaches some of the problems associated with its lack of success and provides statements form leading scientists on the state of the field at that time. The portions of the reference concerned with ethical and political dimensions were not relied upon for the enablement rejection. In addition, the Juicy Whip Inc. v. Orange Bang Inc. decision was based on utility and 35 U.S.C. 101 and not matters of enablement.

(11) Applicant's argue that Eck et al demonstrates that the skilled artisan had a solid basis upon which to make and use the instantly claimed invention. Further, contrary to the Office action, Eck et al is optimistic and provides ample guidance to make and use viral and non-viral gene therapy vectors including a table of NIH approved gene therapy trials.

In response to applicant's arguments, although the Eck reference provides a review of the gene therapy field at the time, the reference also provides for the many obstacles that must be addressed before gene therapy may be successful. Further, the table merely demonstrates that NIH recombinant DNA advisory committee had approved protocols for clinical trials, but does not demonstrate any success rates for these trials. Therefore, Eck et al does not simply provide an optimistic view of gene therapy.

(12) Applicant's argue that the references used in the office action were 4-5 years older than the application and the state of the prior art is what one skilled in the art would have known at the time the application was filed. Further, the state of the

prior art provides evidence for the degree of predictability in the art and is relates to the amount of direction or guidance needed in the specification as filed to meet the enablement requirement and thus the USPTO must evaluate the stat of the prior art fro an application based on its filing date.

In response to applicant's arguments, the Office used the older articles to demonstrate that only a few years prior to filing of the present application that gene therapy was not routine and then used an article at the time of filing to demonstrate that problems with gene therapy still existed.

(13) Applicant's argue that in regard to enablement, the pertinent art is defined in terms of the specific problem to be solved rather than in terms of the technology area for which the invention is used. Further, applicant's argue that all that is required in the instant invention is that the D-type cyclin be introduced into a terminally differentiated cell and induce mitosis and that this is a lesser hurdle to overcome that the other gene therapy trails detailed in Ross et al and Rubanyi. Rubanyi teaches that this has been accomplished in viral systems in human cells. Rubanyi actually supports an embodiment of the invention as enable because of the relative ease of access to the target and the fact that existing gene delivery technology are sufficient to achieve effective expression. Further, Rubanyi states that transient gene expression in some but not in all of the cells in the target is sufficient to yield a therapeutic effect. Applicants further argue that adenoviruses can be produced in high titre, which overcomes one of the concerns raised in the Office action. Finally, Rubanyi teaches that success had

already been seen in models of cardiovascular disease using cyclin and cyclin-dependent kinase inhibitors.

In response to applicant's arguments, the problem to be solved uses a particular technology and therefore, the predictability of the technology must be addressed in term of enablement since it is part of the invention. In regard to success in cardiovascular models, Rubanyi has demonstrated that cardiovascular diseases are "newcomers" as target for human gene therapy, but may be promising for these diseases since temporary expression of the transfected gene in some but all target cells may be necessary to achieve a therapeutic effect. In regard to successes, Rubanyi merely states that promising therapeutic effects have been obtained in animal models of restenosis with the transfer of cyclin or CDK inhibitors, which are used to inhibit cell proliferation. This is not analogous to the claimed invention.

(14) Applicant's argue that Juengst et al is an opinion article. Further, the reference is relied upon to illustrate the "unpredictable nature of the gene therapy", but is not analogous to the instant claims because the gene therapy vector was administered ex vivo to lymphocytes and reintroduced into the patient and patients developed leukemia due to insertion of the transgene at or near the LMO-2 gene. In the instant case, the subpopulation is selected terminally differentiated cells and the target gene is known and only requires transient expression to have a therapeutic effect. In addition, a single example of complications in a clinical trial does not carry enough weight to declare an entire filed as "unpredictable." Finally, Juengst is mostly

concerned with ethical dimensions of clinical trials for gene therapy, which is outside the purview of the USPTO.

In response to applicant's arguments, Juengst was used to demonstrate the unpredictable nature of using viral vectors for gene therapy. Since the instant claims do not limit the invention to transient expression, the use of the Juengst reference is appropriate. For example, the use of other vectors such as retroviral vectors that integrate into the host genome are disclosed in the specification (page 12, paragraph 048). In regard to the clinical trial complication, the complication was important enough to cause the US Food and Drug Administration to halt similar trials in the US and therefore, carries more weight than suggested by applicants. The portions of the reference concerned with ethical dimensions were not relied upon for the enablement rejection.

(15) In regard to the quantity of experimentation, applicants argue that the claims are drawn to D-type cyclins and CDK4 and CDK6 which are known to stimulate mitogenesis and the claims only require that the terminally differentiated cells divide in response to D-type cyclin and CDK, which has been demonstrated by the specification. Further, the standard for enablement is not a "large amount", but an "undue amount of experimentation."

In response to applicant's arguments, the Office acknowledges that the applicants have narrowed the scope of the claimed invention to use only D-type cyclins and CDK 4 or CDK6. In addition, a large amount of experimentation depending on the type required can become "undue experimentation." The phrase "large amount of

experimentation" was taken out of context. In this case, a large of amount of experimentation would have been necessary to determine all the factors necessary to use the claimed gene therapy methods, which ultimately made the experimentation "undue."

(16) Applicant's argue that Rubanyi teaches that "promising therapeutic effects" have been observed in models using cyclin or cyclin dependent kinases. Further, Rubanyi teaches gene therapy for cardiovascular conditions is readily applicable and is only disparaging in more general and ill-defined regiments. The instant invention targets a specific gene (D-type cyclins) and a specific tissue (terminally differentiated cells).

In response to applicant's arguments, Rubanyi merely states that promising therapeutic effects have been obtained in animal models of restenosis with the transfer of cyclin or CDK inhibitors, which are used to inhibit cell proliferation. This is not analogous to the claimed invention. Further, Rubanyi still demonstrates that problems still exist in the field of gene therapy and that the technology is not routine. In regard to the instant invention being specific for D-type cyclins and terminally differentiated cell, the breadth of the claims is actually broad in comparison to the narrow teachings of the specification. In particular, the specification only demonstrates using adenoviral vectors to deliver cyclin D1 and CDK4 to cardiomyocytes, but the claims encompass delivering cyclin D1 and CDK4or CDK 6 using a wide array of vectors and to a wide array of cells.

Claims 1, 2, 4-6 and 16-19 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of proliferating

cardiomyocytes *in vitro* by introducing adenoviral vectors expressing a D-type cyclin, CDK4 or CDK 6 and a nuclear localization signal, does not reasonably provide enablement for an *in vitro or in vivo* method of proliferating any terminal differentiated cell by introducing any cyclin and any cyclin dependent kinase into the cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims for reasons of record as set forth in the office action mailed on November 18, 2005 and above.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tara L Garvey whose telephone number is (571) 272-2917. The examiner can normally be reached on Monday through Friday 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Tara L Garvey, Ph.D.
Examiner
Art Unit 1636

TLG

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